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Reply to Letter to the Editor

Designation of human adenovirus types based on sequence data: An unfinished debate

Dear Editors,

In their letter, Dr. Seto et al. are trying to discredit the serological typing system of human adenoviruses (HAdV): "The report . . . is misleading . . . due to reliance on serological markers . . . which are interpretive, subjective, and error-prone." This remarkable statement contrasts with the opinion of the International Committee on Taxonomy of Viruses (ICTV), presenting the unqualified established serotype definition [1]. Admittedly, HAdV serotyping is not an ideal classification system from a scientific point of view. It was not designed that way but was developed in practice in the clinical framework of infection and immunity. Suboptimal reproducibility between laboratories, dependence on the variable animal origin of antisera, on the kind and condition of the cells used for the VN tests, etc. are inherent to biological assays. Although for technical and economic reasons VN assays are no longer common practice in most clinical virology laboratories, for measuring immunity, identification of clinically relevant characteristics of HAdV, seroprevalence investigations, vaccine studies, and immune interventions they remain indispensable.

Seto et al. reject our designation of our studied HAdV stains as Ad11-14 [2] because "no antisera were made against the putative "11a" viruses nor were HI assays performed." This criticism is based on a misunderstanding. We did not have the ambition of fully describing a new serotype, we just used a standard routine serotyping procedure to further characterize viruses with a HAdV11-like hexon gene and a HAdV14-like fiber gene [2]. Moreover, our results were similar to those of Wigand et al., who did not perform HI tests either, as erythrocytes susceptible to this particular serotype were unavailable (as with us), and who classified virus strain Spain/273/1969 (which was also included in our study) as an antigenically intermediate variant, Ad11-14 [3,4]. At the time, professor Wigand was the director of the German National Reference Centre for Adenoviruses and a highly regarded authority in the field.

The increased availability of sequencing platforms recently encouraged discrepant initiatives – including proposals from Seto et al. – to define and designate HAdVs based on phylogenetic criteria [5–7]. Unfortunately, although nucleotide sequencing is a highly reproducible technique, utilization of the obtained data for taxonomic purposes is not straightforward. Especially because there is still no consensus about criteria for introducing a "new" type. Criteria are anyway difficult to establish and opinions of experts differ [1,5,6]. Since most laboratories lack the resources to sequence complete genomes on large sample sets, any practical phylogenetic typing system should prescribe the specific genes to be used to define a new type. Which genes should be selected, hexon, penton, fiber, all three? How large a difference is required for recognizing a "new" type, 5%, 15%, 25%? Which other properties will be considered, VN and HI assays, oncogenicity, %GC, (all mentioned by the ICTV)? [1] How will differences in these properties be evaluated?

Confusingly, BLAST analysis of hexon and/or fiber gene sequences of intertypic recombinant HAdVs like ours currently returns dual identity matches involving new HAdV types. Up to now at least 16 new HAdV types can be found somewhere. Three types (HAdV52 – 54) are published and have been mentioned by ICTV[1], 9 types (HAdV52 – 58, 61, 65) are published, and 6 types are only traceable in GenBank or UniProt. We could not find any information on HAdV66 anywhere. Some of the "new" viruses are not even available for interested virologists.

The management of the future phylogenetic typing system is still unsettled. Who will decide on the criteria? Who will review and approve claims for new types? Answering these questions is imperative. In the absence of proper control,the number of "new" unreviewed HAdV "types" claimed in the literature or only entered unnoticed in GenBank keeps growing.

Seto et al. deny that the designation HAdV55 is confusing. We think that the various phylogenetic typing systems functioning today are fundamentally confusing. The systems were "grafted" in the existing serotype system by adding consecutively numbered "phylogenetic types" [8–10] to the existing list of 51 serotypes [1,11]. This generated confusion, even more so as the term "serotype" was abandoned and replaced by "type" as if equivalent [7], obscuring the serological basis of the original designation. Interestingly, many of the newly described "types" could be serotyped using a panel of 51 rabbit antisera. For instance, HAdV54 was serotyped as HAdV8 (de Jong et al., unpublished data). This source of confusion could simply be removed by creating a separate numbering system for the phylogenetic types, calling, e.g., HAdV-B52 "HAdV-g1", the "g" standing for "genome". Such solutions should be discussed with an open mind among adenovirologists of various backgrounds. The ideal designation system for HAdV should integrate both serological and molecular typing approaches.

Concerning the current practice, most reported molecular typing data result from partial hexon gene sequencing efforts. Typing approaches targeting the hexon gene [12–14] have provided inexpensive, rapid, and well-correlated molecular surrogates of serological assays, allowing clinical and public health labs to type large numbers of HAdV isolates and, importantly, interpret and analyze data across time and space. Our paper [2] provides additional evidence supporting the use of combined hexon/fiber-based information rather than the whole genome for a meaningful designation for viruses typed by molecular methods.

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